# SAMPLE PREPARATION SYSTEM AND ASSOCIATED APPARATUSES AND METHOD

## FIELD OF THE INVENTION

The present invention relates to a sample preparation system, and more particularly, to a high-throughput system for preparing samples in a multi-well tray and associated apparatuses and method.

## BACKGROUND OF THE INVENTION

Comprehensive functional genomic studies comprise many different procedures such as, for example, phenotypic profiling, gene expression profiling, biochemical profiling, and bioinformatics, wherein each procedure may comprise many sub-procedures. Historically, functional genomic studies require a significant amount of time and labor to complete the necessary tasks and are often characterized by low sample throughput. In some instances, tasks must be serially performed, while in other instances, several tasks may be performed in a parallel manner. Accordingly, scheduling of the required tasks is often a daunting exercise. One of the tasks which may slow the study procedure by lowering throughput and which may hinder efficient scheduling is the preparation of the required samples. Proper preparation of the samples is often critical in obtaining valid study results.

Accordingly, there exists a need for a system capable of preparing profiling samples in a multi-well plate in an expedient and efficient manner. Where sample preparation is directed to providing a certain sample mass in one or more of the wells, such a system should be capable of depositing the sample in the respective well and accurately determining the mass of that sample. Therefore, it would be desirable for such

a system to be capable of preparing the sample with minimal transfer or handling of that sample, while keeping an accurate and modifiable record of each well within a plate, in addition to wells between plates. Further, it would be advantageous for such a system to be automated so as to reduce the necessary amount of manual handling by human operators in preparing the samples. Such automation would also be advantageous where gains in consistency, accuracy, repeatability, and reliability are realized within the sample preparation process. Accordingly, in addition to achieving high throughput in the sample preparation process, such a system would reduce, minimize, or eliminate a typical bottleneck in, for example, a biochemical profiling process, while also reducing personnel costs and labor.

## SUMMARY OF THE INVENTION

The above and other needs are met by the present invention which, in one embodiment, provides a high throughput system for preparing a profiling sample. The system comprises a profiling sample, a plurality of vessels, a plate defining a plurality of receptacles corresponding to, and configured to receive, the plurality of vessels, a dispensing unit for dispensing the profiling sample, and a weighing device. The plurality of receptacles are arranged according to a coordinate system. The dispensing unit has a robotic device in communication therewith, wherein the robotic device is configured according to the coordinate system so as to be registered with the plate. The robotic device is also configured to operably engage the plate so as to dispense a portion of the profiling sample into a selected vessel.

The weighing device also has a robotic device in communication therewith, wherein the robotic device is configured according to the coordinate system so as to be registered with the plate. The robotic device is further configured to operably engage the selected vessel such that, before the portion of the profiling sample is dispensed, the robotic device is capable of removing the selected vessel from the corresponding receptacle of the plate, transferring the selected vessel into operable engagement with the weighing device so as to allow the weighing device to perform a tare measurement of the selected vessel, and then replacing the selected vessel in the corresponding receptacle. After the portion of the profiling sample is dispensed into the selected vessel, the robotic

device and weighing device are capable of cooperating to perform a gross measurement of the selected vessel and the portion of the profiling sample dispensed thereinto using the same procedure for performing the tare measurement. The weight, and thus the mass, of the portion of the profiling sample may then be determined by deducting the tare measurement from the gross measurement of the selected vessel.

Another advantageous aspect of the present invention comprises a high throughput dispensing apparatus adapted to dispense a profiling sample. The apparatus comprises a plurality of vessels, a plate defining a plurality of receptacles corresponding to, and configured to receive, the plurality of vessels, and a dispensing unit for dispensing the profiling sample. The plurality of receptacles is arranged according to a coordinate system. The dispensing unit has a robotic device in communication therewith, wherein the robotic device is configured according to the coordinate system so as to be registered with the plate. The robotic device is also configured to operably engage the plate so as to dispense a portion of the profiling sample into a selected vessel.

Still another advantageous aspect of the present invention comprises a high throughput weight measurement apparatus adapted to prepare a profiling sample. The apparatus comprises a plurality of vessels, a plate defining a plurality of receptacles corresponding to, and configured to receive, the plurality of vessels, and a weighing device. The plurality of receptacles are arranged according to a coordinate system. Further, a robotic device is in communication with the weighing device, wherein the robotic device is configured according to the coordinate system so as to be registered with the plate. The robotic device is also configured to operably engage the selected vessel such that, before a portion of a profiling sample is dispensed into the selected vessel, the robotic device is configured to remove the selected vessel from the corresponding receptacle of the plate and to transfer the selected vessel into operable engagement with the weighing device for the performance of a tare measurement of the selected vessel. The robotic device is further configured to then replace the selected vessel in the corresponding receptacle. After the portion of the profiling sample is dispensed into the selected vessel, the robotic device is configured to remove the selected vessel from the corresponding receptacle of the plate and to transfer the selected vessel into operable engagement with the weighing device for the performance of a gross

measurement of the selected vessel and the portion of the profiling sample disposed therein. The robotic device is further configured to then replace the selected vessel in the corresponding receptacle. A weight, and thus the mass, of the portion of the profiling sample may thereafter be determined by deducting the tare measurement from the gross measurement of the selected vessel.

A further advantageous aspect of the present invention comprises a high throughput method for preparing a profiling sample in at least one selected vessel of a plurality of vessels, wherein the plurality of vessels is received in a plurality of corresponding receptacles defined by a plate and the vessels are arranged according to a coordinate system. First, an automated tare measurement of the selected vessel is performed, independently of the plate, with a weighing device. A portion of the profiling sample is then dispensed into the selected vessel with a dispensing device. Thereafter, a gross measurement of the selected vessel, having the portion of the profiling sample therein, is performed independently of the plate and with the weighing device, wherein the weight, and thus the mass, of the portion of the profiling sample may then be determined as the difference between the gross measurement and the tare measurement of the selected vessel.

Thus, embodiments of the present invention provide a system capable of preparing profiling samples in a multi-well plate in an expedient and efficient manner by implementing a multi-well plate having removable vessels with associated automation. Where sample preparation is directed to providing a certain sample mass in one or more of the wells, such a system is capable of depositing the sample in the respective well and accurately determining the weight of that sample by removing individual vessels from the plate in order to perform the respective weight measurements, from which sample mass may be determined. Since both the dispensing of the sample and the determination of the mass of the dispensed sample is accomplished through the use of one or more robotic devices, such a system is capable of preparing the sample with minimal transfer or handling of that sample. Further, automation allows such a system to keep an accurate and modifiable record of each vessel within a particular plate, in addition to vessels between plates. In addition, the automated system serves to reduce the necessary amount of manual handling of the plate, vessels, and/or sample by human operators when

preparing the vessels and/or sample. Automation of a sample preparation system according to the present invention thereby realizes gains in consistency, accuracy, repeatability, and reliability within the sample preparation process. Accordingly, such a system provides high throughput in the sample preparation process, and thus reduces, minimizes, or eliminates a typical bottleneck in, for example, a biochemical profiling process, while also reducing personnel costs and labor. Thus, embodiments of a sample preparation system and associated apparatuses and method provide significant advantages as detailed further herein.

## BRIEF DESCRIPTION OF THE DRAWINGS

Having thus described the invention in general terms, reference will now be made to the accompanying drawings, which are not necessarily drawn to scale, and wherein:

**FIG. 1** is a schematic representation of a multi-well plate defining a plurality of receptacles for receiving a corresponding plurality of removable vessels in a sample preparation system according to one embodiment of the present invention.

**FIG. 2** is a schematic representation of a high throughput weight measurement apparatus implementing a multi-well plate with removable vessels according to one embodiment of the present invention.

**FIG. 3** is a schematic representation of a high throughput sample dispensing apparatus implementing a multi-well plate with removable vessels according to one embodiment of the present invention.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention now will be described more fully hereinafter with reference to the accompanying drawings, in which preferred embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. Like numbers refer to like elements throughout.

**FIG. 1** provides a schematic representation of a plate having a plurality of removable wells as used in a sample preparation system according to one embodiment of the present invention, the plate being indicated generally by the numeral **100**. As shown, the plate **100** defines a plurality of receptacles **110** configured to receive a corresponding plurality of removable wells, otherwise referred to herein as vessels or minitubes **120**. Such a plate **100** is typically configured to receive, for example, 96 or 384 individual minitubes **120**, in a configuration for laboratory applications, as will be appreciated by one skilled in the art, wherein a Falcon 96 well tube holder, manufactured by Becton Dickinson and Company (Franklin Lakes, New Jersey), is but one example of a plate **100** as referred to herein. It will also be understood that, though the present invention is described herein in terms of 96 or 384 removable wells per plate, the system, apparatuses, and method may also be implemented with appropriate plates having any number of removable wells in accordance with the spirit and scope of the present invention.

Each plate **100** may further include a plate identification indicia **130** comprising, for example, a bar code or other indicia, capable of providing appropriate identification of the plate **100**. In some instances, the individual minitubes **120** may also, or in the alternative to the plate identification indicia **130**, comprise a minitube identification indicia **140** capable of providing appropriate identification of the minitube **120**. Such a minitube identification indicia **140** would be useful, for example, in the event that a minitube **120** becomes separated from, and must be re-united with, the corresponding plate **100**. However, for the sake of brevity, embodiments of the present invention utilizing the plate identification indicia **130** will be described herein, though it will be understood that many different methods and mechanisms, such as the minitube identification indicia **140**, may be used to track and record minitubes within a plate in accordance with the spirit and scope of the present invention. Thus, according to one embodiment of the invention, the receptacles **110** may be arranged within the plate **100** according to a coordinate system, an example of which is generally indicated by the numeral **150**, so as to indicate the location of each minitube **120** within the plate **100**. In such an instance, the plate identification indicia **130** may cooperate with the coordinate system **150** to identify the individual minitubes **120** therein, without requiring the minitube identification indicia **140**.

**FIG. 2** is a schematic representation of a weight measurement apparatus, indicated generally by the numeral **200**, as used in a sample preparation system according to one embodiment of the present invention. The weight measurement apparatus **200** is configured to receive the plate **100** in such a manner that the plate **100** is registered or otherwise aligned with the weight measurement apparatus **200** according to the coordinate system **150** (**FIG. 1**). For example, the plate **100** and the weight measurement apparatus **200** may be configured with each component having respective portions of a mechanically engageable device (not shown), wherein the device, when engaged, would cooperate to align the plate **100** with the weight measurement apparatus **200**. Alternatively, the weight measurement apparatus **200** may include, for example, a computer device **210** in communication with an indicia reader **220** such as, for example, a bar code scanner for reading a bar code. In such an instance, the plate **100** may be configured to become registered with the weight measurement apparatus **200** upon proper engagement therewith and when the indicia reader **220** is capable of reading the plate identification indicia **130**. Upon reading the plate identification indicia **130**, the indicia reader **220** is further configured to send the corresponding information to the computer device **210**, for example, to identify of the plate **100** or to facilitate the establishment of a file, such as a database, corresponding thereto.

The weight measurement apparatus **200** also comprises a robotic device **230** capable of and configured to engage each of the minitubes **120** when the corresponding plate **100** is registered with the weight measurement apparatus **200**. The robotic device **230** is in communication with and controlled by the computer device **210**. Accordingly, upon registration of the plate **100** with the weight measurement apparatus **200** and reading of the plate identification indicia **130** by the indicia reader **220**, the robotic device **230** may be controlled and directed by the computer device **210** to interact with a specific minitube **120** according to the identification thereof, with respect to the coordinate system **150** (**FIG. 1**), as determined by the computer device **210**. To facilitate interaction with a minitube **120**, the robotic device **230** may further comprise an engagement device **240**, also controlled by the computer device **210**, capable of securely engaging the minitube **120** so as to allow the robotic device **230** to remove and replace the minitube **120** with respect to the corresponding receptacle **110** (**FIG. 1**) defined by the plate **100**.

The weight measurement apparatus **200** also comprises a weighing device **250** in communication with the computer device **210**. Such a weighing device **250** may comprise, for example, a Bohdan weighing station produced by the Mettler-Toledo Company (Columbus, Ohio). The weighing device **250** further includes a tube holder **260** configured to receive a minitube **120** transferred from the plate **100**. Accordingly, the computer device **210** is configured to direct the robotic device **230** to engage a minitube **120** with the engagement device **240** and to remove the minitube **120** from the plate **100**. The robotic device **230** is then directed to transfer the minitube **120** into the tube holder **260** of the weighing device **250**. The weighing device **250**, preferably having been calibrated to a zero value with the tube holder **260** in place, is then directed by the computer device **210** to tare, or perform a tare measurement, to determine the weight of the empty minitube **120**. Since the computer device **210** has already determined the identity of the particular minitube **120**, using the identification of the plate **100** from the plate identification indicia **130** and the location of that minitube **120** within the plate **100** according to the coordinate system **150** (**FIG. 1**), one skilled in the art will appreciate that an appropriate database may be prepared or otherwise established so as to allow the identity of that minitube **120**, along with weight measurements and/or other information associated with the minitube **120** to be stored for future use. Upon completion of the tare measurement of the minitube **120**, the robotic device **230** is further configured to remove the minitube **120** from the tube holder **260** and to replace the minitube **120** in the corresponding receptacle **110** in the plate **100**. For a particular plate **100**, the robotic device **230** and the weighing device **250** may be configured to tare any or all of the minitubes **120** and, in some instances, in a particular order or sequence.

**FIG. 3** is a schematic representation of a dispensing apparatus, indicated generally by the numeral **300**, as used in a sample preparation system according to one embodiment of the present invention. The dispensing apparatus **300** is also configured to receive the plate **100** in such a manner that the plate **100** registered or otherwise aligned with the dispensing apparatus **300** according to the coordinate system **150** (**FIG. 1**). Note that, in some instances, the plate **100** may not have to be physically moved from the weight measurement apparatus **200** to the dispensing apparatus **300**, since both the weight measurement apparatus **200** and the dispensing apparatus **300** may be configured

to appropriately engage the plate **100** as disposed at a common site, wherein the plate **100** is registered or otherwise aligned with both apparatuses according to the established coordinate system **150** (**FIG. 1**). The dispensing apparatus **300** further comprises, for example, a computer device **310** in communication with an indicia reader **320** such as, for example, a bar code scanner for reading a bar code. In some instances, the computer device **310** and the indicia reader **320** comprising a portion of the dispensing apparatus **300** may be the same devices as the computer device **210** and the indicia reader **220** comprising a portion of the weight measurement apparatus **200**, respectively. Accordingly, when the plate **100** is engaged and registered with the dispensing apparatus **300**, the indicia reader **320** is capable of reading the plate identification indicia **130**. Upon reading the plate identification indicia **130**, the indicia reader **320** is further configured to send the corresponding information to the computer device **310** such that, for example, the appropriate database for that plate **100** may be accessed, updated, or otherwise modified.

The dispensing apparatus **300** further comprises a robotic device **330** capable of and configured to operably engage each of the minitubes **120** when the corresponding plate **100** is registered with the dispensing apparatus **300**. The robotic device **330** is in communication with and controlled by the computer device **310**. Accordingly, upon registration of the plate **100** with the dispensing apparatus **300** and reading of the plate identification indicia **130** by the indicia reader **320**, the robotic device **330** may be controlled and directed by the computer device **310** to interact, through a dispensing tip **340**, with a specific minitube **120** according to the identification thereof, with respect to the coordinate system **150** (**FIG. 1**), determined by the computer device **310**. In addition, the dispensing apparatus **300** also comprises a dispensing station **350** in communication with the computer device **310** and configured to engage a bulk sample vial **360** containing a profiling sample **370**. The dispensing station **350** may also include an indicia reader **380** configured to read a sample identification indicia **390** associated with the bulk sample vial **360**, the sample identification indicia **390** comprising, for example, a bar code or other indicia. Accordingly, since the profiling sample **370** is to be dispensed into the minitubes **120** of the plate **100** engaged with the dispensing apparatus **300**, the information read from the sample identification indicia **390** by the indicia reader **380** may

be sent to the computer device **310** for association with the database records corresponding to the particular plate **100**.

The robotic device **330** is configured with a dispensing tip **340** which, in one embodiment, is capable of interacting with the profiling sample **370** in the bulk sample vial **360** engaged with the dispensing station **350**. Such a robotic device **330** may comprise, for example, an appropriately modified REDI robot produced by Zinsser Analytic Systems (Frankfurt, Germany). The dispensing tip **340** is directed by the computer device **310** to pick up and retain a predetermined amount or portion of the profiling sample **370** using, for example, a vacuum, a mechanical mechanism, or other suitable device. The computer device **310** is then configured to direct the robotic device **330** to remove the dispensing tip **340** from the bulk sample vial **360** and to move the dispensing tip **340** into operable engagement with a desired minitube **120** in the plate **100**. Once the dispensing tip **340** is in proper engagement with the desired minitube **120**, the computer device **310** directs the dispensing tip **340** to release the retained portion **400** of the profiling sample **370** into the minitube **120**. It will be appreciated by one skilled in the art, however, that many different powdered sample dispensing systems may be implemented to accomplish the desired result of dispensing a predetermined amount or portion of a bulk profiling sample into individual minitubes **120** in accordance with the spirit and scope of the present invention, with the described dispensing apparatus **300** comprising but one such example. For instance, the dispensing apparatus **300** may comprise a powder reservoir having a feed mechanism engaged with a valve device for dispensing a certain amount of the bulk profiling sample into the desired minitube **120**.

The computer device **310** may be further configured to direct the robotic device **330** to dispense a portion of the profiling sample **370** into any or all of the minitubes **120** in the plate **100** and, in some instances, in a desired sequence or order. However, in other instances, the computer device **310** may be configured to leave one or more of the minitubes **120** empty. Accordingly, the selected empty minitubes (not numbered) are appropriately designated as such in the database for the particular plate **100**. These selected empty minitubes (not numbered) may be, for example, directed to receive control samples later dispensed by the robotic device **330** or other dispensing mechanism or may be directed to remain empty so as to comprise physical spacers between other

filled minitubes **120**. It follows that the database for the particular plate **100** may be accessed and updated by the computer device **310** to reflect which minitubes **120** within that plate **100** received a portion of the profiling sample **370** and which minitubes **120** were designated for control samples or the like and left empty.

Referring now to **Figs. 2** and **3**, once the profiling sample dispensing procedure is completed by the dispensing apparatus **300**, the plate **100** is again registered with the weight measurement apparatus **200**. The indicia reader **230**, as previously described, is configured to read the plate identification indicia **130** and to send the corresponding information to the computer device **210** such that the corresponding database for that plate **100** is accessed. Once the individual minitubes **120** are identified by the computer device **210**, the computer device **210** directs the robotic device **230** to remove a selected minitube **120** from the plate **100** and to transfer the minitube **120** to the tube holder **260** of the weighing device **250**. Such a procedure was previously described in conjunction with the taring of the minitubes **120** and will not be further discussed herein. The computer device **210** is thereafter configured to direct the weighing device **250**, calibrated to a zero value, to perform a gross measurement of the weight of the minitube **120** containing a dispensed portion of the profiling sample **370**. The gross measurement is read by the computer device **210**, from the weighing device **250**, and recorded in the corresponding database for the particular minitube **120**. Thus, having previously obtained a tare measurement of a minitube **120** and now the corresponding gross measurement of the same minitube **120** containing a portion of the profiling sample **370**, both measures being saved in a corresponding database, determination of the weight and/or the mass of the portion of the profiling sample **370** is a matter of deducting the tare measurement from the gross measurement, as will be appreciated by one skilled in the art. In some instances, the database may be configured to automatically make such a determination and to save the result as a corresponding record therein.

Note that, the computer device **210** may be configured to direct the robotic device **230** and weighing device **250** to perform a gross measurement of any or all of the minitubes **120**, containing a portion of the profiling sample **370**, in the plate **100**. In some instances, the gross measurement of the minitubes **120** may be performed selectively or according to a predetermined sequence or order. Further, where one or

more selected empty minitubes **120** have been designated, the computer device **210** may be configured to bypass a gross measurement of those empty minitubes **120**. However, if a control sample or other material was deposited within the empty minitubes **120**, the computer device **210** may, in such instances, direct the robotic device **230** and the weighing device **250** to also perform a gross measurement of those minitubes **120**, the gross measurement results being appropriately recorded in the corresponding database for the plate **100**. Note also that, in some instances, a particular desired weight or mass, or range thereof, of the portion of the profiling sample **370** in a minitube **120** may be designated and established as a parameter in the computer device **210**. In such an instance, if the determined weight or mass of the portion of the profiling sample **370** dispensed into a minitube **120** does not correspond to the desired weight, mass, or range thereof, the database and/or computer device **210** may be configured to provide an indication or other alert of the nonconforming sample mass within the minitube **120**, the identity of the corresponding plate **100**, and/or the location of that minitube **120** within the plate **100**. Accordingly, the weight of the portion of the profiling sample **370** within that minitube **120** may then be addressed and adjusted by a manual rework process or, in some instances, in an automated process similar to the dispensing process described herein. In addition, it will be realized and appreciated by one skilled in the art that an appropriate sample preparation system according to one embodiment of the present invention may be defined from the apparatuses and devices described herein. For example, one embodiment of such a sample preparation system may comprise a profiling sample, a removable-well plate housing a plurality of vessels or minitubes, a weight measurement apparatus, and a dispensing apparatus, as previously discussed.

Thus, embodiments of the present invention provide a system capable of preparing profiling samples in a multi-well plate in an expedient and efficient manner by implementing a multi-well plate having removable vessels and corresponding automation for dispensing and determining the weight of powdered sample portions within those vessels. Where sample preparation is directed to providing a certain sample weight or mass in one or more of the wells, such a system is capable of depositing the sample in the respective well and accurately determining the weight of that sample by removing individual vessels from the plate in order to perform the weight measurement thereof.

Since both the dispensing of the sample and the determination of the mass of the dispensed sample are accomplished through the use of one or more robotic devices, such a system is capable of preparing the sample with minimal transfer or handling of that sample. Further, automation allows such a system to keep an accurate and modifiable record of each vessel within a particular plate in addition to vessels between plates. In addition, the automated system serves to reduce the necessary amount of manual handling of the plate, vessels, and/or sample by human operators when preparing the vessels and/or sample. Such automation of a sample preparation system realizes gains in consistency, accuracy, repeatability, and reliability within the sample preparation process, while contemporaneously recording, in a database form, applicable measurements and other information for particular plates and vessels within those plates. The resulting database and information therein may then be supplemented or modified by the results of subsequent tasks of the procedure or other portions of the study, or used to conduct an analysis at the conclusion of the study. Accordingly, such a system provides high throughput in the sample preparation process, and thus reduces, minimizes, or eliminates a typical bottleneck in, for example, a biochemical profiling process, while also reducing personnel costs and labor. Thus, embodiments of a sample preparation system and associated apparatuses and method provide significant advantages as described herein.

Many modifications and other embodiments of the invention will come to mind to one skilled in the art to which this invention pertains having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. For example, the described system may be particularly adapted to handle samples in a liquid form, wherein the appropriate measurement criteria may comprise, for instance, the volume of the portion of the bulk sample within a minitube. Therefore, it is to be understood that the invention is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.